Claims 35, 46-49, 52-55, 61 and 76-78 have been canceled without prejudice.

Amended claims 50 and 64 are supported by original claim 35 and the specification at, for example, page 3, line 32 to page 4, line12; and page 53, lines 13-28.

Amended claim 59 is supported by original claim 61.

Claim 64 has been editorially amended and is supported by the specification at, for example, page 53, lines 23-28.

Claim 68 has been editorially amended and is supported by the specification at, for example, page 1, lines 20-21; page 2, lines 22-29; and page 4, lines 18-21.

Claims 51, 60, 71 and 72 remain unchanged.

Added claims 79-84 are supported by the specification at, for example, page 3, line 32 to page 4, line12; page 46, lines 6-19; page 52, lines 8-9; page 53, lines 19-21; page 54, lines 7-14; page 55, lines 2-12; page 58, lines 3-15; page 58, line 28 to page 59, line 3; and page 59, line 7 to page 61, line 5.

No issues of new mater should arise and entry of the amendment is respectfully requested.

II. Information Disclosure Statement filed April 20, 2000

Applicants respectfully request that the Examiner acknowledge the references cited on the Information Disclosure Statement filed April 20, 2000. A copy of the Information Disclosure Statement, PTO-1449 Form, and April 20, 2000, date-stamped filing receipt are attached hereto as Exhibit 1.

III. Change of Inventorship

Applicants respectfully request that the PTO acknowledge the change of inventorship of the present application pursuant to an Amendment under 37 CFR § 1.48(h) filed July 16, 2001. In the amendment, Tiansheng Wang and Stewart K. Richardson were deleted as inventors.

After entry of the Amendment under 37 CFR § 1.48(h), the inventors of the claims in the present application are David S. Garvey, L. Gordon Letts and Sang William Tam.

IV. First Rejection under 35 U.S.C. §112, First Paragraph

Claims 47-49 and 59-61 are rejected under 35 U. S. C. § 112, first paragraph, as lacking enablement.

Applicants respectfully traverse the rejection and respectfully submit that the claims satisfy the requirements under 35 U.S.C. § 112, first paragraph. Applicants respectfully submit that there is sufficient disclosure for one skilled in the art to use the compositions in the prevention of gastrointestinal disorders without undue experimentation. MPEP 2164.02 states:

> Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph does not turn on whether an example is disclosed.

Applicants respectfully submit that it is well within the capabilities of one skilled in the art to reasonably establish the basis and type of subject to administer the presently claimed compositions to prevent a gastrointestinal disorder. For example, after the administration of the claimed compositions to treat the gastrointestinal disorder one could continue the treatment to "prevent" any future re-occurrences of the gastrointestinal disorder.

As further evidence that one skilled in the art would be able to use the presently claimed compounds and compositions to prevent the claimed gastrointestinal disorders, Applicants direct the Examiner's attention to the prior art references cited in the Office Action as the basis for the rejection of the claims under § 103.

U.S. Patent No. 4,628,098 to Nohara et al, teaches that the proton pump inhibitors described therein are used for ***prophylaxis*** and therapy of digestive ulcers (Nohara at, for example, Abstract and column 6, lines 44-52). Prophylaxis means ***preventing*** disease.[1]

WO 97/25064 states that the compositions comprising proton pump inhibitors and NSAIDs are used in the treatment and ***prophylaxis*** of gastrointestinal disorders associated with the use of Non Steroidal Antiinflammatory Drugs (NSAIDs) (WO 97/25064 at, for example, page 1, lines 5-7). WO 97/25064 teaches that proton pump inhibitors have been shown to ***prevent*** gastric and duodenal erosions in healthy

[1] Webster's New Collegiate Dictionary at page 916 defines prophylaxis as "measures designed to preserve health (as of the body or society) and prevent the spread of disease."

volunteers during treatment with acetyl salicylic acid (WO 97/25064 at page 2, lines 28-30).

U.S. Patent No. 5,380,758 to Stamler et al teaches that "S-nitrosothiols may be used for the treatment or ***prevention*** of gastrointestinal disorders. Disorders of the gastrointestinal tract include achalasia (spasm of the lower esophageal spincter), diarrhea, dumping syndrome and irritable bowel" (Stamler et al at column 9, lines 34-47).

In view of the fact that Nohara and WO 97/25064 teach that proton pump inhibitors are useful in the prevention of certain gastrointestinal disorders, and Stamler teaches that S-nitrosothiols are useful in the prevention of certain gastrointestinal disorders, one skilled in the are would readily believe the teachings in the specification that the claimed compounds and compositions can be used for preventing the claimed gastrointestinal disorders.

The Examiner has not provided any evidence to doubt that the presently claimed compounds and compositions can be used to prevent the claimed gastrointestinal disorders. MPEP 2164.04. In fact, the references cited by the Examiner to reject the claims under § 103 are completely undermined by the rejection of the claims under § 112.

Applicants respectfully submit that the claims satisfy the requirements under 35 U.S.C. § 112, first paragraph, and respectfully request that the rejection under this provision be withdrawn.

V. Rejection under 35 U.S.C. § 112, First Paragraph

Claim 64 has been rejected under 35 U.S.C. § 112, first and second paragraphs, as lacking enablement and as being indefinite.

Applicants respectfully traverse the rejection. Methods for preparing bismuth complexes are disclosed in the specification at, for example, page 53, lines 23-28. In view thereof, Applicants respectfully submit that claim 64 satisfies the requirements under 35 U.S.C. § 112, first and second paragraphs, and respectfully request that the rejection under this provision be withdrawn.

VI. Rejection under 35 U.S.C. § 112, Second Paragraph

Claims 53, 64 and 68 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

Applicants respectfully traverse the rejection. Claim 53 has been canceled without prejudice. Claims 64 and 68 have been editorially amended and are supported by the specification at, for example, page 1, lines 20-21; page 2, lines 22-29; and page 4, lines 18-21. In view thereof, Applicants respectfully submit that the claims satisfy the requirements under 35 USC § 112, and respectfully request that the rejection under this provision be withdrawn.

VII. Rejection under 35 U.S.C. § 103(a)

Claims 35-41, 46-55, 59-61, 64, 66, 68, 71-72 and 76-78 are rejected under 35 U.S.C. § 103 as obvious over Nohara et al. (U.S. Patent No. 4,628,098) or Depui et al (WO 97/25064) in combination with Stamler et al (U.S. Patent No. 5,380,758) in view of Place[2] (U.S. Patent No. 5,403,830); Eek et al[3] (U.S. Patent No. 5,629,305) and Moormann et al.[4] (U.S. Patent No. 5,945,425).

Applicants respectfully traverse the rejection and respectfully submit that there is no motivation to combine the cited references to arrive at the presently claimed invention. Applicants discuss the rejection below as it applies to (i) independent claims 50 and 64 and the claims dependent thereon; (ii) independent claim 59 and the claims dependent thereon; (iii) independent claim 66 and the claims dependent thereon; (iv) claim 51; (v) independent claim 68; and (v) independent claim 71.

A. Independent Claims 50 and 64 and The Claims Dependent Thereon

Claims 35-41, 46-55, 59-61, 64, 66, 68, 71-72 and 76-78 are rejected under 35 U.S.C. § 103 as obvious over Nohara et al. (U.S. Patent No. 4,628,098) or Depui et al (WO 97/25064) in combination with Stamler et al (U.S. Patent No. 5,380,758).

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[2] As it applies to pending claim 51
[3] As it applies to pending claim 68
[4] As it applies to pending claims 54-55 and 71

Nohara discloses certain benzimidazole compounds (e.g., certain proton pump inhibitors), such as lansoprazole, for treating and preventing digestive ulcers and gastritis (Nohura at Abstract; column 1, lines 20-30; column 5, lines 31-43; column 6, lines 44-60).

Nohara does not disclose or suggest a compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase. Nohara does not disclose or suggest the claimed methods for improving the gastroprotective properties, the anti-*Helicobacter pylori* properties, or the antacid properties of a proton pump inhibitor.

Depui discloses formulations comprising a proton pump inhibitor in combination with a non-steroidal anti-inflammatory compound or an antacid formulation and their methods of use for treating and preventing gastrointestinal disorders caused by a non-steroidal anti-inflammatory compound, such as peptic ulceration and dyspeptic symptoms (Depui at pages 1-4).

Dupui does not disclose or suggest a compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase. Dupui does not disclose or suggest the claimed methods for improving the gastroprotective properties, the anti-*Helicobacter pylori* properties, or the antacid properties of a proton pump inhibitor.

Stamler does not disclose or suggest proton pump inhibitors and does not disclose or suggest the claimed methods for improving the gastroprotective properties, the anti-*Helicobacter pylori* properties, or the antacid properties of a proton pump inhibitor.

None of the references disclose or suggest the presently claimed methods for improving the gastroprotective properties, the anti-*Helicobacter pylori* properties, or the antacid properties of a proton pump inhibitor. Since none of the cited references disclose the presently claimed methods, one skilled in the art would not arrive at the presently claimed invention by combining the references.

Moreover, the cited references, individually and in combination, do not disclose, suggest or motivate one to administer a proton pump inhibitor in combination with a compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a

substrate for nitric oxide synthase for improving the gastroprotective properties, the anti-*Helicobacter pylori* properties, or the antacid properties of a proton pump inhibitor, as recited in independent claims 50 and 64 and the claims dependent thereon.

In view thereof, Applicants respectfully submit that the Examiner has not established a *prima facie* rejection with respect to independent claims 50 and 64 and the claims dependent thereon, and respectfully request that the rejection under § 103 be withdrawn as it applies to these claims.

B. Independent Claim 59 and The Claims Dependent Thereon

Claims 35-41, 46-55, 59-61, 64, 66, 68, 71-72 and 76-78 are rejected under 35 U.S.C. § 103 as obvious over Nohara et al. (U.S. Patent No. 4,628,098) or Depui et al (WO 97/25064) in combination with Stamler et al (U.S. Patent No. 5,380,758).

Nohara discloses certain benzimidazole compounds (e.g., certain proton pump inhibitors), such as lansoprazole, for treating and preventing digestive ulcers and gastritis (Nohura at Abstract; column 1, lines 20-30; column 5, lines 31-43; column 6, lines 44-60).

Nohara does not disclose or suggest a compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

Nohara does not disclose or suggest the presently claimed methods for treating or preventing Crohn's disease, ulcerative colitis, a peptic ulcer, a stress ulcers, a bleeding peptic ulcer, a duodenal ulcer, infectious enteritis, colitis, diverticulitis, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, *Helicobacter Pylori* associated disease, short-bowel syndrome, or a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia; for facilitating ulcer healing; or decreasing the recurrence of an ulcer, as recited in independent claim 59 and the claims dependent thereon.

Depui discloses formulations comprising a proton pump inhibitor in combination with a non-steroidal anti-inflammatory compound or an antacid formulation and their methods of use for treating and preventing gastrointestinal disorders caused by a non-steroidal anti-inflammatory compound, such as peptic ulceration and dyspeptic symptoms (Depui at pages 1-4). Depui

discloses NO-releasing non-steroidal anti-inflammatory compounds, i.e., a non-steroidal anti-inflammatory compound that has been chemically modified to link a NO-releasing group (Depui at page 13, line 2). The NO-releasing non-steroidal anti-inflammatory compounds described by Dupui are pro-drugs that are metabolized to the active non-steroidal anti-inflammatory compounds.

Dupui does not disclose or suggest the compounds of the present invention that donate, transfer or release nitric oxide, induce the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulate endogenous synthesis of nitric oxide or are substrates for nitric oxide synthase. Additionally, Dupui does not disclose or suggest the presently claimed methods for treating or preventing Crohn's disease, ulcerative colitis, a peptic ulcer, a stress ulcers, a bleeding peptic ulcer, a duodenal ulcer, infectious enteritis, colitis, diverticulitis, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, *Helicobacter Pylori* associated disease, short-bowel syndrome, or a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia; or for facilitating ulcer healing, or decreasing the recurrence of an ulcer, by administering a proton pump inhibitor compound in combination with a compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

Stamler describes the use of S-nitrosothiol compounds for relaxing gastrointestinal smooth muscles and disorders that are treated by relaxing gastrointestinal smooth muscles. At column 9, lines 34–47, Stamler states (emphasis added):

> Another embodiment of the invention relates to the administration of a therapeutically effective amount of an S-nitrosothiol compound to an animal ***to relax gastrointestinal smooth muscle***. The term "gastrointestinal smooth muscle" refers to smooth muscle which is contained in all areas of the gastrointestinal tract. Such areas include, but are not limited to, the esophagus, duodenum, sphincter of Oddi, biliary tract, ileum, sigmoid colon, panctreatic duct and common bile duct. ***S-nitrosothiols may be used for the treatment or prevention of gastrointestinal disorders. Disorders of the gastrointestinal tract include achalasia (spasm of the lower esophageal sphincter), diarrhea, dumping syndrome and irritable bowel.***

Stamler discloses certain gastrointestinal disorders -- achalasia, diarrhea, dumping syndrome, irritable bowel -- that are treatable by relaxing gastrointestinal smooth muscles.

Stamler does not disclose or suggest the use of S-nitrosothiols for treating or preventing Crohn's disease, ulcerative colitis, a peptic ulcer, a stress ulcers, a bleeding peptic ulcer, a duodenal ulcer, infectious enteritis, colitis, diverticulitis, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, *Helicobacter Pylori* associated disease, short-bowel syndrome, or a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia; or for facilitating ulcer healing, or decreasing the recurrence of an ulcer, as recited in independent claim 59 and the claims dependent thereon.

None of the cited references, individually or in combination, provide any motivation for one to arrive at the presently claimed methods for treating or preventing Crohn's disease, ulcerative colitis, a peptic ulcer, a stress ulcers, a bleeding peptic ulcer, a duodenal ulcer, infectious enteritis, colitis, diverticulitis, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, *Helicobacter Pylori* associated disease, short-bowel syndrome, or a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia; or for facilitating ulcer healing, or decreasing the recurrence of an ulcer, by administering a proton pump inhibitor compound in combination with a compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase, as recited in independent claim 59 and the claims dependent thereon.

In view thereof, Applicants respectfully submit that the Examiner has not established a *prima facie* rejection with respect to independent claim 59 and the claims dependent thereon, and respectfully request that the rejection under § 103 be withdrawn as it applies to these claims.

C. Independent Claim 66 and The Claims Dependent Thereon

Claims 35-41, 46-55, 59-61, 64, 66, 68, 71-72 and 76-78 are rejected under 35 U.S.C. § 103 as obvious over Nohara et al. (U.S. Patent No. 4,628,098) or Depui et al (WO 97/25064) in combination with Stamler et al (U.S. Patent No. 5,380,758).

Nohara discloses certain benzimidazole compounds (e.g., certain proton pump inhibitors), such as lansoprazole, for treating and preventing digestive ulcers and gastritis (Nohura at Abstract; column 1, lines 20-30; column 5, lines 31-43; column 6, lines 44-60).

Nohara does not disclose or suggest a compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

Nohara does not disclose or suggest the presently claimed methods for decreasing or reversing gastrointestinal toxicity or facilitating ulcer healing resulting from administration of a nonsteroidal antiinflammatory drug and/or a selective COX-2 inhibitor, as recited in independent claim 59 and the claims dependent thereon.

Depui discloses formulations comprising a proton pump inhibitor in combination with a non-steroidal anti-inflammatory compound or an antacid formulation and their methods of use for treating and preventing gastrointestinal disorders caused by a non-steroidal anti-inflammatory compound, such as peptic ulceration and dyspeptic symptoms (Depui at pages 1-4). Depui also discloses NO-releasing non-steroidal anti-inflammatory compounds i.e. a non-steroidal anti-inflammatory compound that has been chemically modified to link a NO-releasing group (Depui at page 13, line 2). These compounds are pro-drugs that are metabolized to the active non-steroidal anti-inflammatory compounds.

Dupui does not disclose or suggest the compounds of the present invention that donate, transfer or release nitric oxide, induce the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulate endogenous synthesis of nitric oxide or are substrates for nitric oxide synthase.

Additionally, Dupui does not disclose or suggest the presently claimed methods claimed methods for decreasing or reversing gastrointestinal toxicity or facilitating ulcer healing resulting from administration of a nonsteroidal antiinflammatory drug and/or a selective COX-2 inhibitor, by administering a proton pump inhibitor compound in combination with a compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

Stamler does not disclose or suggest proton pump inhibitors and does not disclose or suggest the claimed methods for decreasing or reversing gastrointestinal toxicity or facilitating ulcer healing resulting from administration of a nonsteroidal antiinflammatory drug and/or a selective COX-2 inhibitor, as recited in independent claim 66 and the claims dependent thereon.

None of the cited references, individually or in combination, provide any motivation for one to arrive at the presently claimed methods for decreasing or reversing gastrointestinal toxicity or facilitating ulcer healing resulting from administration of a nonsteroidal antiinflammatory drug and/or a selective COX-2 inhibitor, by administering a proton pump inhibitor compound in combination with a compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase, as recited in independent claim 66 and the claims dependent thereon.

In view thereof, Applicants respectfully submit that the Examiner has not established a *prima facie* rejection with respect to independent claim 66 and the claims dependent thereon, and respectfully request that the rejection under § 103 be withdrawn as it applies to these claims.

D. Claim 51

Claim 51 is rejected under 35 U.S.C. § 103 as obvious over Nohara et al. (U.S. Patent No. 4,628,098) or Depui et al (WO 97/25064) in view of Place (U.S. Patent No. 5,403,830) and in combination with Stamler et al (U.S. Patent No. 5,380,758).

Applicants respectfully traverse the rejection and respectfully submit that there is no motivation to combine the cited references to arrive at the presently claimed invention.

Place discloses the use of bismuth containing compounds for the treatment of gastrointestinal disorders by administration of H_2 receptor blocking anti-secretory agents, such as cimetidine and ranitidine. Place does not disclose the use of bismuth containing compounds for improving the gastroprotective properties, the anti-*Helicobacter pylori* properties, or the antacid properties of a proton pump inhibitor.

Place does not even disclose or mention a proton pump inhibitor compound or a compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

Place does not provide any motivation for one to use a proton pump inhibitor compound and a bismuth-containing reagent in combination with a compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived

relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase. Thus, Place is non-analogous art and cannot properly form the basis of an obviousness rejection for claims directed to improving the gastroprotective properties, the anti- *Helicobacter pylori* properties, or the antacid properties of a proton pump inhibitor.

Neither Nohara nor Depui disclose or suggest a bismuth-containing reagent. Additionally, there is nothing in Nohara or Depui to motivate one to administer a proton pump inhibitor compound in combination with a bismuth-containing reagent or a proton pump inhibitor alone to improve the gastroprotective properties, the anti-*Helicobacter pylori* properties, or the antacid properties of a proton pump inhibitor. Thus neither Nohara nor Depui disclose, suggest or motivate one to administer a proton pump inhibitor and a bismuth-containing reagent in combination with a compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase for improving the gastroprotective properties, the anti- *Helicobacter pylori* properties, or the antacid properties of a proton pump inhibitor.

The Examiner states that it would be obvious for one to modify Nohara or Dupui in view of Place. Applicants respectfully submit that there is absolutely no motivation to modify Nohara or Depui in view of Place as Place is non-analogous art.

As discussed above Stamler discloses methods to treat gastrointestinal disorders by the administration of a S-nitrosothiol compound. Stamler does not disclose or suggest proton pump inhibitors, bismuth-containing reagents, or the presently claimed methods for improving the gastroprotective properties, the anti- *Helicobacter pylori* properties, or the antacid properties of a proton pump inhibitor. Hence, Stamler cannot motivate one to administering a proton pump inhibitor and a bismuth-containing reagent compound in combination with a compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase for improving the gastroprotective properties, the anti-*Helicobacter pylori* properties, or the antacid properties of a proton pump inhibitor.

None of the cited references disclose or suggest the presently claimed methods for improving the gastroprotective properties, the anti-*Helicobacter pylori* properties, or the antacid

properties of a proton pump inhibitor such that one could not arrive at the presently claimed invention by combining the cited references. In view thereof, Applicants respectfully submit that the claim 51 is unobvious over the combination of cited references, and respectfully request that the rejection under 35 U.S.C. § 103 be withdrawn.

E. Independent Claim 68 and The Claims Dependent Thereon

Claim 68 is rejected under 35 U.S.C. § 103 as obvious over Nohara et al. (U.S. Patent No. 4,628,098) or Depui et al (WO 97/25064) in view of Eek et al (U.S. Patent No. 5,629,305) and in combination with Stamler et al (U.S. Patent No. 5,380,758).

Applicants respectfully traverse the rejection and respectfully submit that there is no motivation to combine the cited references to arrive at the presently claimed invention.

Applicants respectfully submit that none of the cited references disclose, suggest or motivate one to use a compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase for the treatment of an infection resulting from *Helicobacter pylori.*

Eek does not disclose or suggest a compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

Nohara does not disclose or suggests the use of a compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase for the treatment of an infection resulting from *Helicobacter pylori.*

Depui does not discloses or suggests the use of proton pump inhibitors or a compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase for the treatment of the treatment of an infection resulting from *Helicobacter pylori.*

Stamler does not discloses or suggests the use of proton pump inhibitors or a compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide

or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase for the treatment of an infection resulting from *Helicobacter pylori.*

Hence, the cited references cannot properly form the basis of an obviousness rejection for method claims directed to the treatment of an infection resulting from *Helicobacter pylori* by the administration of an acid degradable antibacterial compound, a proton pump inhibitor compound and a compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

In view thereof, Applicants respectfully submit that the claims 53 and 68 are unobvious over the combination of cited references, and respectfully request that the rejection under 35 U.S.C. § 103 be withdrawn.

F. Independent Claim 71 and The Claims Dependent Thereon

Claim 71 is rejected under 35 U.S.C. § 103 as obvious over Nohara et al. (U.S. Patent No. 4,628,098) or Depui et al (WO 97/25064) in view of Moormann et al (U.S. Patent No. 5,945,425) and in combination with Stamler et al (U.S. Patent No. 5,380,758).

Applicants respectfully traverse the rejection and respectfully submit that there is no motivation to combine the cited references to arrive at the presently claimed invention.

Applicants respectfully submit that none of the cited references disclose, suggest or motivate one to use a compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase for the treatment of a viral infection.

Moormann does not disclose or suggest a compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

Nohara does not disclose or suggest the use of a proton pump inhibitor or a compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide

or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase for the treatment of a viral infection.

Depui does not disclose or suggest the use of proton pump inhibitors or a compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase for the treatment of a viral infection.

Stamler does not disclose or suggest the use of proton pump inhibitors or a compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase for the treatment of a viral infection.

Hence, the cited references cannot properly form the basis of an obviousness rejection for method claims directed to the treatment of a viral infection by the administration of a proton pump inhibitor compound and a compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

In view thereof, Applicants respectfully submit that independent claim 71 and the claims dependent thereon are unobvious over the combination of cited references, and respectfully request that the rejection under 35 U.S.C. § 103 be withdrawn.

VIII. Duplicate Claim Warning

A. Claims 59-61 are assertedly a duplicate of claims 47-49.

Applicants respectfully disagree because the claims are clearly not the same. Claims 47-49 generally recite the administration of a composition. Claims 59-61 generally recite the administration of either a composition or two separate compounds. Accordingly, claims 47-49 and claims 59-61 are not duplicates of each other.

B. Claim 64 is assertedly a duplicate of claim 51.

Applicants respectfully disagree because the claims are clearly not the same. Claim 51 generally recites administration of a proton pump inhibitor in combination with a bismuth-containing reagent. Claim 64 generally recites administration of bismuth complexes of the proton pump inhibitor. Accordingly, claims 51 and 64 are not duplicates of each other.

C. Claim 66 is assertedly a duplicate of claim 52.

Applicants respectfully disagree because the claims are not the same. Claim 52 generally recites the administration of a composition. Claim 66 generally recites the administration of two separate compounds. Accordingly, claims 52 and 66 are not duplicates of each other.

D. Claim 68 is assertedly a duplicate of claim 53.

Applicants respectfully disagree because the claims are not the same. Claim 53 generally recites the administration of one compound and a composition. Claim 68 generally recites the administration of either three separate compounds; one composition; or one compound and one composition. Accordingly, claims 53 and 68 are not duplicates of each other.

E. Claims 71-72 are assertedly duplicates of claims 54-55.

Applicants respectfully disagree because the claims are clearly not the same. Claim 54-55 generally recite the administration of a composition. Claims 71-72 generally recite the administration of either a composition or two separate compounds. Accordingly, claims 47-49 and claims 59-61 are clearly not duplicates of each other.

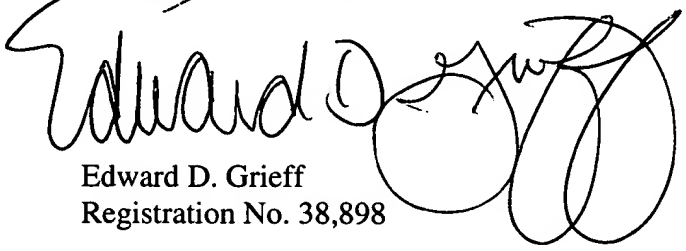
Applicants respectfully submit that no pending claims are duplicates of another pending claim. Accordingly, no objection should be made against the claims upon a finding of allowable subject matter.

IX. Conclusion

Applicants respectfully request reconsideration and allowance of pending claims 36-45, 50, 51, 59, 60, 64, 66, 68, 71, 72 and 79-84.

Examiner Rao is encouraged to contact the undersigned at 202-942-8453 concerning any questions about the present application.

Respectfully submitted



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Dated: December 13, 2001

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Appendix 2 – Marked-up Copy of Amendment to the Title

Please amend the Title of the Invention as follows:

[NITROSATED AND NITROSYLATED] METHODS USING PROTON PUMP INHIBITORS[, COMPOSITIONS] AND NITRIC OXIDE DONORS [METHODS OF USE]